IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Bisoprolol fumarate Pinewood 3.75 mg Film-coated tablet
BISOPROLOL FUMARATE
PA0281/264/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Bisoprolol fumarate Pinewood 1.25mg 2.5mg 3.75 mg 5mg 7.5mg 10mg Film-coated tablet, from Pinewood Laboratories Ltd on 16th February 2024 for:
the treatment of of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1)

This is a standard abridged (generic) application submitted under Article 10(1) of Directive 2001/83/EC authorised via a decentralised procedure (DCP) IE/H/1237/001-006/DC with Ireland (HPRA) as RMS and Malta the only CMS.

This medicinal product will be subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Bisoprolol fumarate Pinewood 3.75mg Film-coated tablet
Name(s) of the active substance(s) (INN)	Bisoprolol Fumarate
Pharmacotherapeutic classification (ATC code)	C07AB07
Pharmaceutical form and strength(s)	3.75mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/264/003
Marketing Authorisation Holder	Pinewood Laboratories Ltd
MRP/DCP No.	IE/H/1237/003/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Bisoprolol fumarate Pinewood 1.25mg 2.5mg 3.75 mg 5mg 7.5mg 10mg Film-coated tablet.

II.2 Drug substance

The active substance is Bisoprolol fumarate an established active substance described in the European/British Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film coated tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg or 10 mg of bisoprolol fumarate.

The excipients in the medicinal products are listed in section 6.1 of the SmPC.
A visual description of the products is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Bisoprolol fumarate Pinewood 1.25mg 2.5mg 3.75 mg 5mg 7.5mg 10mg Film-coated tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Cardicor on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

Pharmacodynamic, pharmacokinetic and toxicological properties of Bisoprolol Fumarate are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Bisoprolol fumarate Pinewood 1.25/2.5/3.75/5.0/7.5/10 mg film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

As Bisoprolol Fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bisoprolol Fumarate is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product, Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg, 10mg film coated tablets PA2286/004/001-0006, marketed by MAH: Merck Serono (Ireland) Limited

For this generic application, the applicant has submitted two single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence studies in which the pharmacokinetic profile of the test product Bisoprolol fumarate Pinewood 3.75 mg and 10mg Film-coated tablets (IPCA Laboratories Limited, India) is compared with the pharmacokinetic profile of the reference product Cardicor® (Bisoprolol Fumarate Tablets) 3.75mg and 10mg of Merck Sereno Ltd. Bedfont cross, Stanwell Road, Feltham, Middlesex UK.

As per EU guidance, bioequivalence study should be conducted with the highest strength in linear pharmacokinetics, however the developed formulation is non-linear with highest strength 10 mg, hence a separate BE study for 3.75 mg was performed.

Based on the pharmacokinetic parameters of active substance, the reference tablets Cardicor 3.75mg and 10mg film coated tablets marketed by Merck Sereno Ltd and test tablets Bisoprolol fumarate Pinewood 3.75mg and 10mg Film-coated tablets (IPCA Laboratories Limited, India) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The bioequivalence studies for 7.5 mg, 5mg, 2.5mg and 1.25mg strengths of Bisoprolol fumarate tablets can be waived. The applicant has provided justification to support the bioequivalence studies and to confirm the adequacy of the biowaivers of these strengths.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption

Bisoprolol is absorbed and has a biological availability of about 90% after oral administration.

Distribution

The distribution volume is 3.5 l/kg. The plasma protein binding of bisoprolol is about 30%.

Biotransformation and Elimination

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Total clearance is approximately 15 l/h. The half-life in plasma of 10-12 hours gives a 24 hour effect after dosing once daily**.**

IV.3 Pharmacodynamics

The pharmacodynamics of Bisoprolol Fumarate are well established and adequately discussed in the clinical overview.
Pharmacotherapeutic group: Beta blocking agents, selective
ATC-code: C07AB07

IV.4 Clinical Efficacy

As Bisoprolol Fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The clinical overview on the efficacy is thus, appropriate for this abridged (generic) application submitted under Article 10(1) of Directive 2001/83/EC.

IV.5 Clinical Safety

As Bisoprolol Fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The clinical overview on the safety is thus, appropriate for this abridged (generic) application submitted under Article 10(1) of Directive 2001/83/EC.

Please see the accompanying product information for full prescribing details including safety information on contraindications, warnings, interactions and possible side effects.

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bisoprolol fumarate Pinewood Tablets.

Safety specification

Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance and risk minimisation activities are sufficient to identify, characterise, prevent or minimise risks relating to Bisoprolol fumarate Pinewood Tablets.

Periodic Safety Update Report (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Abridged applications submitted under Article 10(1) of Directive 2001/83/EC avoid the need for repetitive tests on humans. For these applications the bioequivalence studies are pivotal and the applicant has submitted two single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence studies in which the pharmacokinetic profile of the test product Bisoprolol fumarate Pinewood 3.75 mg and 10mg Film-coated tablets (IPCA Laboratories Limited, India) is compared with the pharmacokinetic profile of the reference product Cardicor® (Bisoprolol Fumarate Tablets) 3.75mg and 10mg of Merck Sereno Ltd. Bedfont cross, Stanwell Road, Feltham, Middlesex UK.

Based on the pharmacokinetic parameters of active substance, the reference tablets Cardicor 3.75mg and 10mg film coated tablets marketed by Merck Sereno Ltd and test tablets Bisoprolol fumarate Pinewood 3.75mg and 10mg Film-coated tablets (IPCA Laboratories Limited, India) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The bioequivalence studies for 7.5 mg, 5mg, 2.5mg and 1.25mg strengths of Bisoprolol fumarate tablets can be waived. The applicant has provided justification to support the bioequivalence studies and to confirm the adequacy of the biowaivers of these strengths.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product, Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg, 10mg film coated tablets PA2286/004/001-0006, marketed by MAH: Merck Serono (Ireland) Limited.

V. OVERALL CONCLUSIONS

Bisoprolol fumarate Pinewood 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg Film-coated tablets are a generic form of Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg Film-coated tablets which are a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Bisoprolol fumarate Pinewood 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg Film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

15.02.2029